AMENDMENTS TO THE CLAIMS

Please amend claims 10, 16, 17, 19, 20, 22, 24, 26 and 41 as follows:

Claim 1 (Original) A method for identifying ligands or aptamers specific for a membrane receptor protein-tyrosine kinase (RPTK), expressed in an activated or nonactivated form, by cells, using a mixture of nucleic acids, which method comprises at least the following steps:

(a) bringing a mixture of nucleic acids into contact with cells not expressing said receptor protein-tyrosine kinase or expressing it in a nonactivated form (C_N cells), said cells having the same cell type as cells expressing the same receptor protein-tyrosine kinase but in an activated form, due to the existence of a mutation in the extracellular domain (C_{Te} cells);

(b) recovering a first subset S1 of nucleic acids which do not bind to the C_N cells, in step (a);

(c) bringing said first subset S1 into contact with C_i cells, having the same cell type as the C_{Te} cells, but expressing said receptor protein-tyrosine kinase mutated in its intracellular part, said C_i cells exhibiting a phenotype of the same type as that of the C_{Te} cells;

(d) recovering a second subset S2 of nucleic acids which do not bind to the C_i cells in step (c);

(e) bringing the second subset S2 into contact with the C_{Te} cells;

(f) recovering the nucleic acids which bind to said C_{Te} cells, i.e. those exhibiting a high affinity with respect to the cells expressing said receptor protein-tyrosine kinase mutated in the extracellular domain, after dissociation of the cell-nucleic acid complexes;

(g) amplifying said nucleic acids with high affinity for the cells expressing said receptor protein-tyrosine kinase mutated in the extracellular domain, so as to obtain a mixture of nucleic acids, enriched in nucleic acids having a high affinity for said C_{Te} cells, and

(h) identifying the ligands or aptamers specific for the cells expressing receptor protein-tyrosine kinases (RPTKs) in an activated form, from the mixture obtained in (g).

Claim 2 (Previously Presented) The method as claimed in claim 1, wherein steps (a)-(g) are repeated using the mixtures enriched in ligands or aptamers from the preceding cycle, until at least one aptamer is obtained, the affinity of said aptamer, defined by its dissociation constant (Kd), can be measured and is suitable for pharmaceutical use.

Claim 3 (Previously Presented) The method of claim 1 wherein the starting nucleic acid combinatorial library contains at least 10^2 nucleic acids.

Claim 4 (Previously Presented) The method of claim 3, wherein said starting nucleic acid combinatorial library consists of nucleic acids comprising random sequences each containing between 10 and 1000 nucleotides.

Claim 5 (Previously Presented) The method of claim 1 wherein the identification of the ligands or aptamers specific for the C_{Te} cells according to step (h) comprises an evaluation of the biological activity of said aptamers on said C_{Te} cells.

Claim 6 (Previously Presented) The method of claim 5, wherein said biological activity which is evaluated comprises the following:

(a) inhibition or activation of the auto-phosphorylation of the RPTK,

(b) inhibition or activation of the kinase activation cascade,

(c) inhibition of the phosphorylation of the normal RPTK of C_N cells activated by suitable stimulation, and

(d) reversion of the phenotype associated with activation of the RPTK.

Claim 7 (Previously Presented) An aptamer, wherein said aptamer is specific for cells expressing a receptor protein-tyrosine kinase (RPTK) in an activated or nonactivated form and can be identified by the method for identifying aptamers of claim 1.

Claim 8 (Previously Presented) The aptamer as claimed in claim 7, wherein the receptor protein-tyrosine kinase (RPTK) in an activated or nonactivated form, is selected from the group consisting of: EGFR (Epithelial Growth Factor Receptor), InsulinR (Insulin Receptor), PDGFR (Platelet-derived Growth Factor Receptor), VEGFR (Vascular Endothelial Growth Factor Receptor), FGFR (Fibroblast Growth Factor Receptor), NGFR (Nerve Growth Factor Receptor), HGFR (Hepatocyte Growth Factor Receptor), EPHR (Ephrin Receptor), AXL (Tyro 3 PTK), TIE (Tyrosine Kinase Receptor in endothelial cells), RET (Rearranged During Transfection), ROS (RPTK expressed in certain epithelial cells) and LTK (Leukocyte Tyrosine Kinase).

Claim 9 (Previously Presented) The aptamer as claimed in claim 7 wherein said aptamer recognises a Ret receptor in an activated form.

Claim 10 (Currently Amended) The aptamer as claimed in claim 9, wherein said aptamer can be identified by means of the method comprising:

(a) bringing a mixture of nucleic acids into contact with C_N cells not expressing any Ret receptor in an activated form,

(b) recovering a first subset S1 of nucleic acids which do not bind to said C_N cells, in step (a),

(c) bringing said first subset S1 into contact with C_i cells expressing a Ret receptor, mutated in its intracellular domain,[[,]]

(d) recovering a second subset S2 of nucleic acids which do not bind to said C_i cells,

(e) bringing the second subset S2 into contact with C_{Te} cells expressing a Ret receptor activated by mutation in the extracellular domain, which receptor is selected from the group consisting of mutated Ret receptors carrying a mutation on one of the cysteines located in the extracellular domain,[[r,]]

(f) recovering the nucleic acids bound to said C_{Te} cells, exhibiting both a high affinity and a binding specificity for the cells expressing a mutated Ret receptor as defined in step (e),

(g) amplifying said nucleic acids obtained in step (f), to obtain a mixture of nucleic acids, enriched in nucleic acids having a high affinity for the C_{Te} cells,

(h) repeating steps (a)-(g), until at least one aptamer is obtained, the affinity of which for the C_{Te} cells, defined by its dissociation constant (Kd), is measurable and suitable for a pharmacological activity, and

(i) identifying the aptamers specific for the cells expressing a Ret receptor in its activated form, selected from the mixture obtained in (h).

Claim 11 (Previously Presented) The aptamer as claimed in claim 10, wherein

- the C_N cells are wild-type PC12 cells (reference ECACC No. 88022) or wild-type NIH 3T3 cells (reference ECACC No. 93061524),
- the C_i and C_{Te} cells are obtained by introducing an oncogene bearing a mutation, respectively intracellular and extracellular, in C_N cells in culture such that the latter express the oncogene.

Claim 12 (Previously Presented) An aptamer, wherein said aptamer can be obtained by the method of claim 1 and is selected from the group consisting of the aptamers of formula (I):

$$R_1\text{-}R\text{-}R_2 \qquad (I),$$

in which:

R_1 represents 5' GGGAGACAAGAAUAAACGCUCAA 3' (SEQ ID NO:1) or a fragment of 1 to 23 nucleotides of said SEQ ID NO:1;

R_2 represents 5' AACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:2) or a fragment of 1 to 24 nucleotides of said SEQ ID NO:2, and

R represents a random sequence of 10 to 1000 nucleotides.

Claim 13 (Previously Presented) The aptamer as claimed in claim 12 wherein R is selected from the following sequences:

D4	5'GCGCGGGAAUAGUAUGGAAGGAUACGUAUACCGUGCAAUCCAGGGCAACG 3' (SEQ ID NO:3)
D12	5'GGGCUUCAUAAGCUACACCGGCCAACGCAGAAAUGCCUUAAGCCCGAGUU 3' (SEQ ID NO:4)
D14	5'GGCCAUAGCGCACCACCAAGAGCAAAUCCCUAAGCGCGACUCGAGUGAGC 3' (SEQ ID NO:5)
D20	5'GGGCCAAUCGAAGCCGGUAAUUCCCAAACUAACGUGCAAACUGCACCCGC 3' (SEQ ID NO:6)
D24	5'GCGGUAUGUAGGGAAUAGCACUUUUUUUGCGUAUACCUACACCGCAGCG 3' (SEQ ID NO:7)
D30	5'AGGCGAGCCCGACCACGUCAGUAUGCUAGACAACAACGCCCGCGUGGUAC 3' (SEQ ID NO:8)
D32	5'CCCCGCUUUUUGACGUGAUCGAACGCGUAUCAGUAACGUCAGCAGUCGAGC 3' (SEQ ID NO9)
D33	5'CAAAGCGUGUAUUCUCGUGAGCCGACCAUCGUUGCGAACAUCCCCCGGAACG 3' (SEQ ID NO :10)
D42	5'GACCCGUAUGAAGGUGGCGCAGGACACGACCGUCUGCAAUGAGCGAGC 3' (SEQ ID NO:11)
D60	5'CCGACCUGUACAGCAGUUAGUUACACGUUUGAAACAACCGGCGUUCGAGC 3' (SEQ ID NO:12)
D76	5'GGCUUACACGGAGAAACAAGAGAGCGGCCCAAACUUGAUUGACAGUGGCC 3' (SEQ ID NO:13)
D71	5'GGCCCUUAACGCAAAAACGAAGGAUCAUCGAUUGAUCGCCUUAUGGGCU 3' (SEQ ID NO:14)
D87	5'CCGCGGUCUGUGGGACCCUUCAGGAUGAAGCGGCAACCCAUGCGGGCC 3' (SEQ ID NO:15)

Claim 14 (Previously Presented) The aptamer as claimed in claim 12 wherein the riboses of the purines bear a hydroxyl function on the carbon in the 2'-position, while the riboses of the pyrimidines bear a fluorine atom on the carbon in the 2'-position.

Claim 15 (Previously Presented) The aptamer as claimed in claim 12 wherein said aptamer has one of the following sequences: SEQ ID NOs:31-33.

Claim 16 (Currently Amended) The aptamer as claimed in claim 12, wherein said aptamer has formula II below:

5'$R_4X_6X_5X_4X_3$GGAAUAG$X_2X_1R_3X'_1X'_2$CGUAUAC$X'_3X'_4X'_5X'_6R_5$3' (SEQ ID NO: 34)

(II), wherein:

- the riboses of the purines bear an OH group in the 2'-position and the riboses of the pyrimidines bear a fluorine atom in the 2'-position;
- **R_3** is present or absent and represents an apical bulge comprising:
  - a linear or branched carbon chain selected from the group consisting of C_6-C_{30} alkyl groups and C_6-C_{30} aryl groups;
  - a polymer selected from the group consisting of PEG and PEI[[,]];
  - functional groups selected from the group consisting of biotin, streptavidin, and peroxidase;
  - other molecules of interest selected from the group consisting of active ingredients, labeling tags, and chelating agents for radioisotopes;
  - a natural or modified nucleotide sequence;[[;]]
- **X_1, X'_1, X_2, X'_2, X_3, X'_3, X_4, X'_4, X_5, X'_5, X_6 and X'_6** represent Py or Pu with,

  X_1-X'_1 corresponding to C-G, A-U, G-C or U-A

  X_2-X'_2 corresponding to C-G, A-U, G-C or U-A

X_3-X'_3 corresponding to C-G, A-U, G-C or U-A

X_4-X'_4 corresponding to C-G, A-U, G-C or U-A

X_5-X'_5 corresponding to C-G, A-U, G-C or U-A

X_6-X'_6 corresponding to C-G, A-U, G-C or U-A

N corresponding to G or C or A or U,

Pu corresponding to G or A, in which the riboses bear an OH group in the 2'-position,

Py corresponds to U or C, in which the riboses bear a fluorine atom in the 2'-position, and

- $\mathbf{R_4}$ and $\mathbf{R_5}$ are present or absent and represent:

. a natural or modified nucleotide sequence, comprising between 1 and several thousand nucleotides, wherein a part of said nucleotide sequence is selected from the group consisting of the following sequences:

R_4 :

5'-R_1-Z_1-3', with Z_1=G:

5' GGGAGACAAGAAUAAACGCUCAAG 3' (SEQ ID NO:18),

5'-R_1-Z_1-3', with Z_1=GCGGUAU (SEQ ID NO:26):

5' GGGAGACAAGAAUAAACGCUCAAGCGGUAU (SEQ ID NO:19), and

R_5 :

5'-Z_2-R_2-3', with Z_2=CAAUCCAGGGCAACG (SEQ ID NO:27):

5'CAAUCCAGGGCAACGAACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:20)

5'-Z_2-R_2-3', with Z_2=ACCGCAGCG (SEQ ID NO:28):

5' ACCGCAGCGAACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:21),

5' GGGAGACAAGAAUAAACGCUCAAG 3' (SEQ ID NO:18)

5' GGGAGACAAGAAUAAACGCUCAAGCGGUAU (SEQ ID NO:19), for R_4

and

5' CAAUCCAGGGCAACGAACGACAGGAGGCUCACAACAGGA 3' (SEQ I D NO: 20) and

5' ACCGCAGCGAACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:21) for R_5;

- a linear or branched carbon chain selected from the group consisting of C_6-C_{30} alkyl groups, C_6-C_{30} aryl groups
- a polymer selected from the group consisting of PEG and PEI;
- functional groups selected from the group consisting of biotin, streptavidin and peroxidase;
- other molecules of interest, selected from the group consisting of active ingredients, labeling tags,[[,]] and chelating agents for radioisotopes.

Claim 17 (Currently Amended) The aptamer as claimed in claim 16, wherein R_3 represents 5' UGGAAGGA 3' (SEQ ID NO: 29) (loop (1)), R_4 represents SEQ ID NO:18 and R_5 represents SEQ ID NO:20, said aptamer has both properties of binding to a Ret receptor and properties of inhibition of the activity of said receptor.

Claim 18 (Previously Presented) The aptamer as claimed in claim 17, wherein said aptamer has the sequence SEQ ID NO:22.

Claim 19 (Currently Amended) The aptamer as claimed in claim 16, wherein R_3 represents 5' CUUUUUU 3' (SEQ ID NO: 30) (loop (2)), 5' GNPuA 3' (loop (3)) or 5' UNCG 3' (loop (4)), R_4 comprises from 1 to 30 nucleotides selected from SEQ ID NO:19 or from 1 to 24

nucleotides selected from SEQ ID NO:18 and R_5 comprises from 1 to 33 nucleotides of SEQ ID NO:21 or from 1 to 39 nucleotides selected from SEQ ID NO:20, the aptamer of this structure having only properties of binding to a Ret receptor in its activated or nonactivated form.

Claim 20 (Currently Amended) The aptamer as claimed in claim 19, wherein R_3 represents 5' CUUUUUU 3' (SEQ ID NO: 30), R_4 represents SEQ ID NO:19 and R_5 represents SEQ ID NO:21.

Claim 21 (Previously Presented) The aptamer as claimed in claim 19 wherein said aptamer has SEQ ID NO:25.

Claim 22 (Currently Amended) The aptamer as claimed in claim 16 wherein said aptamer has the sequence SEQ ID NO:23 and R_3 represents 5' UGGAAGGA 3' (SEQ ID NO: 29), R_4 and R_5 are absent, the aptamer of this structure having only properties of binding to a Ret receptor in its activated or nonactivated form.

Claim 23 (Previously Presented) A reagent for diagnosing a tumor, wherein said reagent comprises an aptamer as claimed in claim 12.

Claim 24 (Currently Amended) The reagent as claimed in claim 23, comprising an aptamer of formula II:

5'$R_4X_6X_5X_4X_3$GGAAUAG$X_2X_1R_3X'_1X'_2$CGUAUAC$X'_3X'_4X'_5X'_6R_5$3' (SEQ ID NO: 35) (II), in which R_3, R_4 and R_5 are absent.

Claim 25 (Previously Presented) The reagent as claimed in claim 24, comprising an aptamer of sequence:

5' GUAGGGAAUAGCACGUAUACCUAC 3' (SEQ ID NO:24).

Claim 26 (Currently Amended) The reagent as claimed in claim 23, comprising an aptamer of formula II, $5'R_4X_6X_5X_4X_3GGAAUAGX_2X_1R_3X'_1X'_2CGUAUACX'_3X'_4X'_5X'_6R_53'$ (SEQ ID NO: 34) (II), in which R_3 represents 5' CUUUUUU 3' (SEQ ID NO: 30), said aptamer corresponding to the sequence SEQ ID NO:25.

Claim 27 (Previously Presented) A reagent for diagnosing or detecting a Ret receptor in an activated or nonactivated form, comprising at least one aptamer as claimed in claim 12.

Claim 28 (Previously Presented) A medicament, comprising an aptamer as claimed in claim 7, which has both an ability to bind to an RPTK receptor and an inhibitory action with respect to said receptor in an activated form.

Claim 29 (Previously Presented) A medicament for use in the treatment of a tumor, wherein the medicament comprises an aptamer as claimed in claim 7 which has both an ability to bind to an activated RPTK receptor and an inhibitory action with respect to this receptor.

Claim 30 (Previously Presented) The medicament as claimed in claim 28 comprising an aptamer selected from the group consisting of the aptamers of formula (I):

$$R_1\text{-}R\text{-}R_2 \qquad (I),$$

in which:

R_1 represents 5' GGGAGACAAGAAUAAACGCUCAA 3' (SEQ ID NO:1) or a fragment of 1 to 23 nucleotides of said SEQ ID NO:1;

R_2 represents 5' AACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:2) or a fragment of 1 to 24 nucleotides of said SEQ ID NO:2, and

R represents SEQ ID NO. 3.

Claim 31 (Previously Presented) A pharmaceutical composition, comprising an aptamer as claimed in claim 7 which has both an ability to bind to an RPTK receptor and an inhibitory action with respect to said receptor in its activated form.

Claim 32 (Previously Presented) A pharmaceutical composition, comprising:

- an aptamer as claimed in claim 7, which has both an ability to bind to an activated RPTK receptor mutated in the extracellular domain, and an inhibitory action with respect to this mutated receptor,
- another anticancer molecule, and
- at least one pharmaceutically acceptable vehicle.

Claim 33 (Previously Presented) The use of an aptamer which has both an ability to bind to an RPTK receptor and an inhibitory action with respect to this RPTK receptor, for screening products which interact with the RPTK receptor and which may or may not inhibit it comprising:

- bringing cells expressing RPTKs in an activated or nonactivated form into contact with the product to be tested,
- adding, under suitable conditions, an aptamer of claim 7, before, at the same time as or after the product to be tested,

- evaluating the competitive binding between the aptamer and the product to be tested.

Claim 34 (Previously Presented) The use of an aptamer which has both an ability to bind to an activated RPTK receptor mutated at one of the cysteines located in the extracellular domain (codons 609, 611, 618, 620 and 634), and an inhibitory action with respect to this activated RPTK receptor, for screening products which interact with said RPTK receptor, comprising:

- bringing cells expressing RPTKs in an activated or nonactivated form into contact with the product to be tested,
- adding, under suitable conditions, an aptamer of claim 7, before, at the same time as or after the product to be tested,
- evaluating the competitive binding between the aptamer and the product to be tested.

Claim 35 (Previously Presented) A method for screening products which interact with an RPTK receptor or targets which form a complex with said RPTK in an activated or nonactivated form, which method comprises:

- bringing cells expressing RPTKs in an activated or nonactivated form into contact with the substance to be tested,
- adding, under suitable conditions, an aptamer of claim 7, before, at the same time as or after the substance to be tested,
- evaluating the competitive binding between the aptamer and the molecule to be tested.

Claim 36 (Previously Presented) The method as claimed in claim 35, wherein after identification of the substances which bind competitively with the aptamer to the cells exhibiting RPTKs, the effect of these substances on the biological activity of said cells can be evaluated in

order to find substances which inhibit or activate biological activities of the cells exhibiting RPTKs.

Claim 37 (Previously Presented) The method of claim 1 wherein the starting nucleic acid combinatorial library contains nucleic acids comprising random sequences characterized by respectively at their 5' and 3' ends having fixed sequences for PCR amplification.

Claim 38 (Previously Presented) The aptamer as claimed in claim 9 wherein said aptamer recognises the Ret receptor activated by mutation at a cysteine located in the extracellular domain.

Claim 39 (Previously Presented) The aptamer as claimed in claim 9 wherein said aptamer recognises the Ret receptor activated by mutation at a cysteine located at codons 609, 611, 618, 620 or 634.

Claim 40 (Previously Presented) The aptamer as claimed in claim 13 wherein the riboses of the purines bear a hydroxyl function on the carbon in the 2'-position, while the riboses of the pyrimidines bear a fluorine atom on the carbon in the 2'-position.

Claim 41 (Currently Amended) The aptamer as claimed in claim 14 wherein said aptamer has formula II below:

5'$R_4X_6X_5X_4X_3$GGAAUAG$X_2X_1R_3X'_1X'_2$CGUAUAC$X'_3X'_4X'_5X'_6R_5$3' (SEQ ID NO: 34) (II), wherein:

- the riboses of the purines bear an OH group in the 2'-position and the riboses of the pyrimidines bear a fluorine atom in the 2'-position;

- **R_3** is present or absent and represents an apical bulge comprising:
  - a linear or branched carbon chain selected from the group consisting of C_6-C_{30} alkyl groups and C_6-C_{30} aryl groups,
  - a polymer selected from the group consisting of PEG and PEI,
  - functional groups selected from the group consisting of biotin, streptavidin and peroxidase,
  - other molecules of interest selected from the group consisting of active ingredients, labeling tags and chelating agents for radioisotopes,
  - a natural or modified nucleotide sequence;
- **X_1, X'_1, X_2, X'_2, X_3, X'_3, X_4, X'_4, X_5, X'_5, X_6 and X'_6** represent Py or Pu with

  X_1-X'_1 corresponding to C-G, A-U, G-C or U-A

  X_2-X'_2 corresponding to C-G, A-U, G-C or U-A

  X_3-X'_3 corresponding to C-G, A-U, G-C or U-A

  X_4-X'_4 corresponding to C-G, A-U, G-C or U-A

  X_5-X'_5 corresponding to C-G, A-U, G-C or U-A

  X_6-X'_6 corresponding to C-G, A-U, G-C or U-A

  N corresponding to G or C or A or U,

  Pu corresponding to G or A, in which the riboses bear an OH group in the 2'-position,

  Py corresponds to U or C, in which the riboses bear a fluorine atom in the 2'-position, and
- **R_4** and **R_5** are present or absent and represent:
  - a natural or modified nucleotide sequence, comprising between 1 and several thousand nucleotides, wherein a part of said nucleotide sequence is selected from the group consisting of the following sequences:

R_4 :

5'-R_1-Z_1-3', with Z_1=G:

5' GGGAGACAAGAAUAAACGCUCAAG 3' (SEQ ID NO:18),

5'-R_1-Z_1-3', with Z_1=GCGGUAU (SEQ ID NO:26):

5' GGGAGACAAGAAUAAACGCUCAAGCGGUAU (SEQ ID NO:19), and

R_5 :

5'-Z_2-R_2-3', with Z_2=CAAUCCAGGGCAACG (SEQ ID NO:27):

5'CAAUCCAGGGCAACGAACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:20)

5'-Z_2-R_2-3', with Z_2=ACCGCAGCG (SEQ ID NO:28):

5' ACCGCAGCGAACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:21),

5' GGGAGACAAGAAUAAACGCUCAAG 3' (SEQ ID NO:18)

5' GGGAGACAAGAAUAAACGCUCAAGCGGUAU (SEQ ID NO:19), for R_4 and

5' CAAUCCAGGGCAACGAACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO: 20) and

5' ACCGCAGCGAACGACAGGAGGCUCACAACAGGA 3' (SEQ ID NO:21) for R_5;

a linear or branched carbon chain selected from the group consisting of C_6-C_{30} alkyl groups, and C_6-C_{30} aryl groups;

a polymer selected from the group consisting of PEG and PEI;

functional groups selected from the group consisting of biotin, streptavidin and peroxidase;

other molecules of interest selected from the group consisting of active ingredients, labeling tags and chelating agents for radioisotopes.

Claim 42 (Previously Presented) A pharmaceutical composition, comprising:

- an aptamer as claimed in claim 7 , which has both an ability to bind to Ret receptor mutated at one of the cysteines located in the extracellular domain (codons 609, 611, 618, 620 and 634), and an inhibitory action with respect to this mutated receptor,
- another anticancer molecule, and
- at least one pharmaceutically acceptable vehicle.

Claim 43 (Previously Presented) The aptamer as claimed in Claim 16, wherein R_3 represents bulges selected from the group consisting of (1) to (4):

loop (1): 5' UGGAAGGA 3' (SEQ ID NO:29)

loop (2): 5' CUUUUUU 3' (SEQ ID NO:30)

loop (3): 5' GNPuA 3' and

loop (4): 5' UNCG 3',

in which the riboses of the purines bear a hydroxyl function on the carbon in the 2' position, while the riboses of the pyrimidines bear a fluorine atom on the carbon in the 2'-position.

Claim 44 (Previously Presented) The aptamer as claimed in Claim 41, wherein R_3 represents bulges selected from the group consisting of (1) to (4):

loop (1): 5' UGGAAGGA 3' (SEQ ID NO:29)

loop (2): 5' CUUUUUU 3' (SEQ ID NO:30)

loop (3): 5' GNPuA 3' and

loop (4): 5' UNCG 3',

in which the riboses of the purines bear a hydroxyl function on the carbon in the 2' position, while the riboses of the pyrimidines bear a fluorine atom on the carbon in the 2'-position.

Claim 45 (Previously Presented) The method of Claim 1 wherein the starting nucleic acid combinatorial library contains nucleic acids comprising the sequences SEQ ID NO:1, SEQ ID NO:2 or a fragment of at least 8 nucleotides of these sequences.